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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,657	02/04/2005	Stefano Carlino	LABM-10	9578

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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,657	CARLINO, STEFANO	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's amendment/ remarks/ response filed 06 July, 2007, wherein claims 3 have been cancelled and claims 1 and 6 have been amended. Claims 1-2 and 4-9 are currently pending and are examined on the merits herein.

Rejections Withdrawn

In view of the cancellation of claim 3, all rejections made with respect to claim 3 in the previous office action are withdrawn.

The rejection under 35 U.S.C § 112, second paragraph with respect to the lack of lower limits of claims 1-9 is withdrawn since the applicants have amended the claims to include a lower limit of 0.1μm in claims 1 and 6, and the cancellation of claim 3 which included the limitation "less than 200 millibars".

The following is a new ground of rejection/ objection necessitated by applicants' amendments:

Claim Objections

Claim 4 is objected to because of the following informalities: The word "according" is misspelled as "acing". Claim 4 depends from the cancelled claim 3. Appropriate correction is required.

The following are new or modified rejections necessitated by Applicant's amendment filed 06/07/07, wherein the limitations in pending claims 1 and 6 as

amended now have been changed and claims 2 and 5-9 depend from claim 1. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, mailed 03/06/07, have been modified and are listed below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 and 4-6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 7 and 8-10 of U.S. Patent No. 6,489,467. (Of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the

'467 patent claims a process for purifying high molecular weight hyaluronic acid (HA) comprising the steps of filtering a solution comprising the steps of filtration of a solution comprising HA followed by concentrating or freeze drying.

The '467 patent claims a process in which HA through a filter with a pore size in the range from 100,000 Daltons nominal molecular weight cut-off to 0.45 μm. (Column 9, Claim 1). The '467 patent claims a method further comprising a step of concentrating the filtered solution. (Column 10, Claim 10, lines 1-5) and a process of freeze drying the sterilized solution.

The '467 patent does not expressly use the step of concentrating filtered aqueous formulation by applying vacuum.

It would have been obvious to one of skill in the art to apply vacuum to concentrate the filtered solution of HA. Selecting vacuum method to concentrate a solution is considered a routine step within the knowledge of one of ordinary skill in the art.

Response to Arguments

Applicant's arguments filed 06/07/07 have been fully considered but they are not persuasive. Applicants argue that the previously reported methods of preparing ready-to-use pharmaceutical formulations require the steps of "involve measuring a defined precise quantity by weight of hyaluronic acid that is mixed with a precise volume of water and precise quantities of excipients". This argument was found unpersuasive since the claims herein recite the open transitional phrase "comprising" that allows the inclusion of other steps.

The applicants further argue that, an alternative process for preparing ready-to-use hyaluronic acid pharmaceutical formulations reported in US Patent No. 5,093,487, involves filtering a concentrated solution of hyaluronic acid aqueous formulation by means of multiple passes through a 0.2 µm filter reduces the viscosity of the hyaluronic acid. However, the rejections herein were not based on the '487 patent and viscosity is not claimed as an element in the application herein. The above double patenting rejection is considered proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlino et. al. (WO 00/44925; Of Record) in view of Sakuma et. al. (EP 0631799 A1; Of Record).

Carlino et. al. discloses a process for purifying high molecular weight hyaluronic acid. (Abstract). The molecular weight of HA was disclosed as more than $5x10^5$ Daltons, overlapping with the 800,000 to 5,000,000 Daltons range claimed herein. (Page 3, paragraph 4). Filter of 0.2µm is disclosed. (Page 7,

paragraph 6-7). Carlino further discloses a monitoring of optical density of the solution during filtration. (Page 7, last paragraph to page 8 first paragraph). Carlino further discloses adjustment of pH by addition of NaOH after filtration. (Page 8, Paragraph 5; Page 10, paragraph 8). This is considered a step of adding excipients that affect conductivity. The filtration process is considered a sterilization step. (Page 10, Paragraph 6-7).

Carlino does not expressly disclose the use of vacuum to boil off water.

Sakuma et. al. discloses a vacuum concentration plant. (Abstract). The vacuum concentration plant is disclosed as useful for concentration enzymes and protein solutions. (Page 3, liens 5-12). Sakuma et. al. discloses that the process is useful for concentrating solutions sensitive to heat. (Page 3, paragraphs 3-5). Sakuma et. al. further discloses method for adjusting pressure in vacuum vapor generator. (Page 6, lines 20-35). A procedure for concentrating liquids using vacuum concentration plant is further described. (Page 6 line 36-Page 7, line 2). It is considered within the capabilities of one of skill in the art in their routine activities to choose the appropriate settings for pressure and settings to determine the liquid level to stop the vacuum concentration step or to measure the concentration using a spectrophotometer, or to measure and adjust conductivity, all techniques well known and routine in biological and biochemical arts. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt at a specified concentration comprising the steps of providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration, passing said aqueous formulation through a filter having a pore size less than 0.45μm and concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached.

One of ordinary skill in the art would have been motivated to use a vacuum concentration method to concentrate the filtered HA solution as claimed herein, because the process of purifying HA by filtration is described by Carlino et. al. and Sakuma et. al. discloses a method for concentrating solutions including proteins and enzymes by vacuum concentration that has the advantage of concentrating solutions at low temperatures.

Therefore, one of ordinary skill in the art would have reasonably expected that the use of sterile filtration followed by vacuum filtration would result in concentrated solutions of HA.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 06/07/07 have been fully considered but they are not persuasive. Applicants argue that the previously reported methods of

preparing ready-to-use pharmaceutical formulations require the steps of "involve measuring a defined precise quantity by weight of hyaluronic acid that is mixed with a precise volume of water and precise quantities of excipients". This argument was found unpersuasive since the claims herein recite the open transitional phrase "comprising" that allows the inclusion of other steps. Applicant further argue that the "inventor of the present application has developed, for the first time, a process which enables the provision of sterile ready-to-use pharmaceutical formulations of high molecular weight HA that can be directly filled into syringes or vials for pharmaceutical use directly from the process "reactor," with no further preparation or sterilization required before use." The claims herein include the steps of filtering HA solution and concentrating the filtered solution. As discussed above, filtration is considered a method of sterilization. Using vacuuming to reduce volume of aqueous solutions is a well-known basic technique in organic, biochemical and pharmaceutical arts. Since filtration itself is a sterilization process no "further preparation or sterilization is required before use". Measuring ingredients accurately and calculating concentrations from added ingredients and measured volumes and spectral measurements are all basic skills of those in the pharmaceutical arts. The term ready-to-use is construed to include any type of use. Applicants further argue that one of ordinary skill in the art would find it necessary to prepare a purified sterile concentrated powder of sodium hyaluronate in view of WO 00/44925. However, the claims herein do not preclude the use of sterile concentrated powder to make an aqueous formulation of HA. Applicants further argue that EP

0631799 is not concerned with preparation of pharmaceutical formulations and that it is designed for bulk concentration of liquids. The claims herein are not limited by any specific quantity. As noted above, the vacuum concentration plant is disclosed as useful for concentration enzymes and protein solutions. (Page 3, liens 5-12). Furthemore, the use of vacuum to adjust volume in an aqueous solution is considered a basic skill of one of ordinary skill in the art. As such, the rejection under 103(a) is still deemed proper and is adhered to.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

8/31/07

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